UK- 427,857 (maraviroc)

Drug Class: **Entry and Fusion Inhibitors**

Drug Description

UK-427,857 is a chemokine receptor antagonist that acts as an entry inhibitor. It is designed to prevent HIV infection of CD4 cells by blocking the CCR5 coreceptor from binding to HIV. [1]

HIV/AIDS-Related Uses

UK-427,857 is an investigational entry inhibitor that binds to a protein on the membrane of T cells called CCR5. The CCR5-tropic variant of the virus is common in earlier HIV infection, so UK-427,857 may be most useful in acute and early infection.[2]

Pharmacology

UK-427,857 binds to the CCR5 receptor, preventing HIV from binding to this receptor. When the CCR5 receptor is unavailable, CCR5-tropic HIV cannot engage a CD4 cell to infect the cell. The CCR5-tropic variant of the virus is common in earlier HIV infection, while viruses adapted to use the CXCR4 receptor gradually become dominant as HIV infection progresses. Thus, UK-427,857 may be most useful in acute and early infection, but further studies are needed.[3]

In a small Phase I study from 2003, 24 HIV infected adults with CCR5-tropic HIV were randomized to receive 25 mg UK-427,857 once daily, 100 mg twice daily, or placebo. Steady state drug levels were reached within 7 days, with more favorable drug levels acheived in the fasted state. By Day 14, those receiving 100 mg doses had experienced a viral load decline of more than 20-fold, compared to a nearly 3-fold reduction in the 25 mg group. The drug was well tolerated, and viral load did not rebound immediately upon cessation of the drug, indicating that a proportion of the receptors remain blocked for some time.[4]

A second placebo-controlled Phase I study of UK-427,857 demonstrated greater viral load declines with monotherapy than with placebo. Based on the results of this study, the researchers recommend a dose of 100 mg twice daily or higher be used. A similar study comparing a range of doses also showed viral load reductions of more than 10-fold at doses above 100 mg once or twice daily, with no effect of food on the drug's antiviral efficacy.[5]

It is not known if the CCR5 protein on T cells or HIV can become resistant to UK-427,857 or how quickly such resistance could develop.[6] In an in vitro study using six primary CCR5 HIV-1 isolates, those able to replicate in the presence of high UK-427,857 concentrations emerged gradually after multiple passages of all isolates. Two isolates resistant to UK-427,857 continued to use the CCR5 receptor and one isolate developed the ability to use the CXCR4 receptor. In the viruses that remained R5-tropic, two different sets of mutations developed in the gp120 V3 loop region; this and other data suggest that changes in viral tropism are independent of UK-427,857.[7] [8] All CCR5 antagonists bind to CCR5 in a pocket formed by transmembrane helices and extracellular loop 2 (ECL2); it appears that subtle differences in occupation of the binding pocket may block replication of some HIV strains. As a result, scientists are optimistic that resistance to an HIV coreceptor antagonist will not necessarily lead to drug class resistance.[9]

Adverse Events/Toxicity

In 80 HIV infected adults, UK-427,857 was well tolerated.[10] In another Phase I study enrolling 54 HIV uninfected adults taking 100 or 300 mg UK-427,857 twice daily, no adverse effects were observed on white or red blood cell counts or any other blood tests.[11]

In a study of UK-427,857's effects on the QTc interval, single doses of UK-427,857 (at doses of 100, 300, or 900 mg) were given to healthy volunteers. Dizziness was reported when UK-427,857 was given at a 900 mg single dose; other side effects reported from this study include headache, postural hypotension, nausea, and cystitis.[12]

Drug and Food Interactions

In a small Phase I study, UK-427,857's antiviral effectiveness against HIV was unaffected by

UK- 427,857 (maraviroc)

Drug and Food Interactions (cont.)

food.[13]

In HIV infected adults, a dose of 150 mg UK-427,857 twice daily following a high fat meal was evaluated in order to assess the effect of food on antiviral efficacy. UK-427,857's plasma concentrations were similar to those seen in healthy volunteers under similar food restrictions.[14]

A four-cohort study, with administration of single doses of UK-427,857, was conducted in 29 HIV infected people who were stable for 3 months on one of four protocol-chosen antiretroviral regimens. Cohort 1 received efavirenz, abacavir sulfate, and lamivudine; cohort 2 received efavirenz, didanosine, and tenofovir disoproxil fumarate (tenofovir DF); cohort 3 received nevirapine, lamivudine, and tenofovir DF; and cohort 4 received lopinavir/ritonavir, stavudine, and lamivudine. Participants received a single oral dose of UK-427,857; serial blood draws were conducted over 12 hours post-dose. Results suggested that taking UK-427,857 with regimens containing efavirenz led to an approximately 50% reduction in UK-427,857. Conversely, UK-427,857 exposure doubled in the cohort receiving lopinavir/ritonavir. Additional dose adjustment studies are needed to determine optimal dosages for UK-427,857, especially when taken with other antiretrovirals.[15]

Clinical Trials

For information on clinical trials that involve UK-427,857 (maraviroc), visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: UK-427,857 (maraviroc) AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[16]

Dosage Form: UK-427,857 has been studied at doses of 25, 50, 100, 150, 300, and 900 mg.[17] [18] Once- and twice-daily administrations of UK-427,857 have been studied.[19]

Further Reading

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Manufacturer Information

UK-427,857 (maraviroc)
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
(800) 438-1985

For More Information

Contact your doctor or an AIDSinfo Health

For More Information (cont.)

Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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